Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.6399-20
Intern Med 60: 1963-1969, 2021
http://internmed.jp

【 CASE REPORT 】

The First Case of Eosinophilic Granulomatosis with Polyangiitis Simultaneously Demonstrating Various Clinical Manifestations with Retroperitoneal Fibrosis and Membranous Nephropathy

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Abstract:
The first case of eosinophilic granulomatosis with polyangiitis (EGPA) simultaneously demonstrating various clinical manifestations, including retroperitoneal fibrosis (RPF) causing hydronephrosis and membranous nephropathy (MN) leading to nephrotic syndrome, is presented. There have been no previous case reports demonstrating the simultaneous onset of these three disease categories with significant complex pathologies. This case was successfully managed by providing adequate combination therapies according to each disease category, leading to complete remission (CR) of all three diseases. In conclusion, we believe this case is extremely rare and clinically suggestive, and that these findings can be applied to a future phenotype-tailored treatment strategy for EGPA.

Key words: eosinophilic granulomatosis with polyangiitis, retroperitoneal fibrosis, membranous nephropathy, simultaneous onset

(Intern Med 60: 1963-1969, 2021)
(DOI: 10.2169/internalmedicine.6399-20)

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), also known as Churg-Strauss syndrome, is a disseminated necrotizing small-vessel vasculitis with extravascular granulomas containing eosinophils, and such patients frequently develop allergic sinusitis and asthma (1). Although there have been some clinical guidelines and treatment recommendations for managing EGPA, large knowledge gaps have remained, particularly with regard to the pathophysiologic and diagnostic uncertainties based on the heterogeneous clinical manifestations of EGPA (2). Furthermore, EGPA is a conceptually difficult disorder given its dual categorization of a hypereosinophilic syndrome and systemic vasculitide, as well as the absence of a specific biomarker, such as antineutrophil cytoplasmic antibodies (ANCA) (3). Phenotype-tailored therapies are still poorly understood, and no phenotype-specific therapeutic strategy has yet been established.

We herein report unique case of EGPA with mononeuritis multiplex simultaneously developing both retroperitoneal fibrosis (RPF) causing hydronephrosis and membranous nephropathy (MN) leading to nephrotic syndrome. Although there have been no previous case reports demonstrating the simultaneous onset of these three disease categories, this case was successfully managed by providing adequate combination therapies according to each disease category, leading to complete remission (CR) of all three diseases. We believe that this case is very rare and clinically suggestive with a unique onset of three associated diseases and that the findings can be applied to the development of a phenotype-tailored treatment strategy for EGPA.

Case Report

A 50-year-old woman was admitted to our hospital in early September with a history of left-sided abdominal pain

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Received: September 29, 2020; Accepted: December 6, 2020; Advance Publication by J-STAGE: February 1, 2021
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Table. Laboratory Data on Admission.

<Blood cell count>		<Biochemical examination>	
white blood cells	16,240 /μL	C3	69 mg/dL
eosinophils	1,300 /μL	C4	10.9 mg/dL
blood hemoglobin	9.5 g/dL	CH50	14 mg/dL
platelet count	9.5×10^4 /μL	immunoglobulin G	1,416 mg/dL
<Blood coagulation>		immunoglobulin G4	37 mg/dL
partial thromboplastin time	12.2 S	immunoglobulin A	513 mg/dL
activated partial thromboplastin time	31 S	immunoglobulin M	85 mg/dL
D-dimer	2.2 μg/mL	immunoglobulin E	574.7 U/mL
<Urinalysis>		antinuclear antibody	(-)
proteinuria	8.39 g/day (SI=0.08)	antineutrophil cytoplasmic antibodies	(-)
glycosuria	(-)	immunoelectrophoretic study	no myeloma protein
occult blood	(+)	anti-phospholipase A2 receptor antibody	(-)
<Biochemical examination>		<Infectious screeing>	
total protein	5 g/dL	hepatitis B virus antigen	(-)
serum albumin	1.3 g/dL	hepatitis B virus antibody	(-)
lactate dehydrogenase	219 U/L	hepatitis B core antigen	(-)
aspartate aminotransferase	16 U/L	hepatitis C virus antibody	(-)
alanine aminotransferase	9 U/L	serological tests for syphilis	(-)
low-density lipoprotein cholesterol	110 mg/dL	treponema pallidum hemagglutination	(-)
triglyceride	164 mg/dL	anti-human immunodeficiency virus antigen/antibody	(-)
blood urea nitrogen	5.1 mg/dL		
serum creatinine	0.54 mg/dL	cytomegalovirus antibody	(-)
sodium	134 mEq/L	interferon-gamma release assay	(-)
potassium	4.3 mEq/L	beta-D-glucan	<6.0 mg/dL
chloride	98 mEq/L	procalcitonin	0.1 ng/dL
c-reactive protein	11.89 mg/dL	<Tumor marker>	
glycated hemoglobin (HbA1c)	5.7 %	carcinoembryonic antigen	1.1 ng/mL
		carbohydrate antigen 19-9	21.8 U/mL

since late July and edema of the lower extremities with massive proteinuria, as well as mild numbness and weakness of the left lower leg, left hand, and right toe since mid-August. She had been diagnosed at her previous hospital with RPF based on the typical findings on computed tomography (CT) of the abdomen in early August. Because nephrotic syndrome was suspected as the cause of the edema of the lower extremities since mid-August, she was referred to our hospital in early September. Her history included hysterectomy for uterine fibroids at 33 years of age, 3 operations for mammary papillomas at 40 years of age, bronchial asthma at 48 years of age, and sinusitis at 50 years of age. She had been applying estradiol gel every day for two years and received a placental extract injection once a week for three years for menopausal disorders until July. She had a family history of gastric cancer but no family history of renal disease.

On admission, her vital signs were normal (blood pressure 114/75 mmHg, heart rate 79 beats/min, and temperature 37.0°C). Her physical examination showed edema of the lower extremities and mild numbness and weakness of the left lower leg, left hand, and right toe.

Major laboratory examinations on admission showed the following: white blood cells, 16,240/μL; eosinophils, 1,300/μL; hemoglobin, 9.5 g/dL; platelet count, 9.5×10^4/μL; partial thromboplastin time, 12.2 seconds; activated partial thromboplastin time, 31.0 seconds; D-dimer, 2.2 μg/mL; total protein, 5.0 g/dL; serum albumin, 1.3 g/dL; lactate dehydrogenase, 219 U/L; aspartate aminotransferase, 16 U/L; alanine aminotransferase, 9 U/L; low-density lipoprotein cholesterol, 110 mg/dL; triglycerides, 164 mg/dL; blood urea nitrogen, 5.1 mg/dL; serum creatinine, 0.54 mg/dL; sodium, 134 mEq/L; potassium, 4.3 mEq/L; chloride, 98 mEq/L; C-reactive protein, 11.89 mg/dL; glycated hemoglobin (HbA1c), 5.7%; C3, 69 mg/dL; C4, 10.9 mg/dL; hemolytic complement activity (CH50), 14 mg/dL; immunoglobulin (Ig) G, 1,416 mg/dL; immunoglobulin (Ig) G 4, 37 mg/dL; IgA, 513 mg/dL; IgM, 85 mg/dL; IgE, 574.7 U/mL; antinuclear antibody, (-); antineutrophil cytoplasmic antibodies, (-); anti-phospholipase A2 receptor (anti-PLA2R) antibody, (-); hepatitis B virus antigen, (-); hepatitis B virus antibody, (-); hepatitis B core antigen, (-); hepatitis C virus antibody, (-); anti-human immunodeficiency virus antigen/antibody, (-); cytomegalovirus antibody, (-); interferon-gamma release assay, (-); beta-D-glucan, <6.0 mg/dL; and procalcitonin, 0.1 ng/dL. A urinalysis showed the following: proteinuria, 8.39 g/day; glycosuria, (-); occult blood, (+); and urinary protein selectivity, 0.08. An immunoelectrophoretic study showed no myeloma protein (Table).

CT of the abdomen showed left hydronephrosis and an ir-

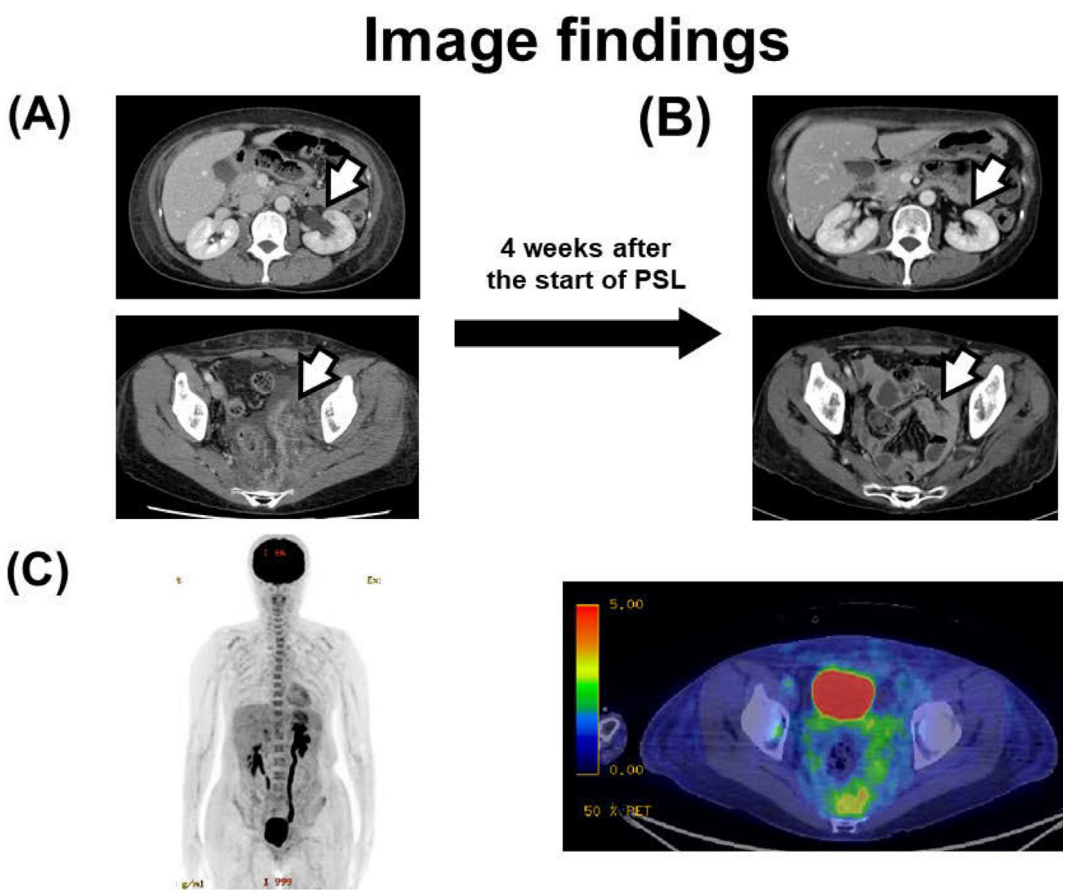

Figure 1. **Imaging findings. (A) Computed tomography (CT) of the abdomen shows left hydronephrosis (up image) and an irregular mass in the retroperitoneum from the left side of the pelvis to around the rectum (lower image). (B) CT findings four weeks after the start of PSL. Disappearance of left hydronephrosis and the irregular mass (↓ , arrow). (C) ^{18}F-deoxyglucose positron emission tomography (FDG-PET) shows the accumulation of FDG in conformity with the irregular mass but not in other parts.**

regular mass in the retroperitoneum from the left side of the pelvis to around the rectum (Fig. 1A). ^{18}F-deoxyglucose positron emission tomography (FDG-PET) showed the accumulation of FDG in conformity with the irregular mass but not in other parts (Fig. 1C). The biopsy results of the irregular mass showed fibrous tissue with inflammatory cell infiltration containing eosinophils, with no malignant tumors. There were no atypical lymphocytes, no granulomatous lesions, and no IgG4-positive plasma cells (Fig. 2A). In addition, there was no history of drugs or underlying diseases (collagen disease, abdominal aortic aneurysm, infection, trauma) that might cause RPF. Based on these results, a definitive diagnosis of RPF was made.

It was necessary to search for the causes of the advanced proteinuria and edema of the lower extremities. Therefore, a percutaneous renal biopsy was performed. Light microscopy showed 18 glomeruli, none of which were globally or segmentally sclerotic and had cellular crescents. No infiltrate of IgG4-positive plasma cells was found in the interstitium. Periodic acid-Schiff (PAS) stain showed normal mesangial matrix and no mesangial hypercellularity. Periodic acid-methenamine-silver (PAM) stain did not show marked widespread thickening of the capillary walls or spike formation (Fig. 2B). Immunofluorescence microscopy, however, showed diffuse and granular capillary wall staining for IgG (+) and C3 (+) (Fig. 2D). The IgG deposits with IgG subclass staining (IgG1, IgG2, IgG3, and IgG4) were predominantly IgG4>IgG1 (Fig. 2E). Electron microscopy confirmed the presence of extensive subepithelial deposits in the capillary membranes. Finally, a definitive diagnosis of MN, Churg classification stage 2, was made based on the electron microscopic findings (Fig. 2C).

A nerve conduction study (NCS) was performed for the numbness and weakness of the left lower leg, left hand, and right toe. A reduced amplitude of compound muscle action potentials (CMAPs) was more noticeable than a reduced conduction velocity, and polyneuropathy due to vasculitis was diagnosed. In addition, the presence of eosinophilia (≥ 1,500 cells observed since mid-August at another hospital), eosinophilic infiltration into retroperitoneal tissue, sinusitis, and bronchial asthma met the American College of Rheumatology (ACR) criteria and the Lanham criteria for EGPA (4, 5). Therefore, a definitive diagnosis of EGPA was made. The vasculitis activity was determined using the Bir-

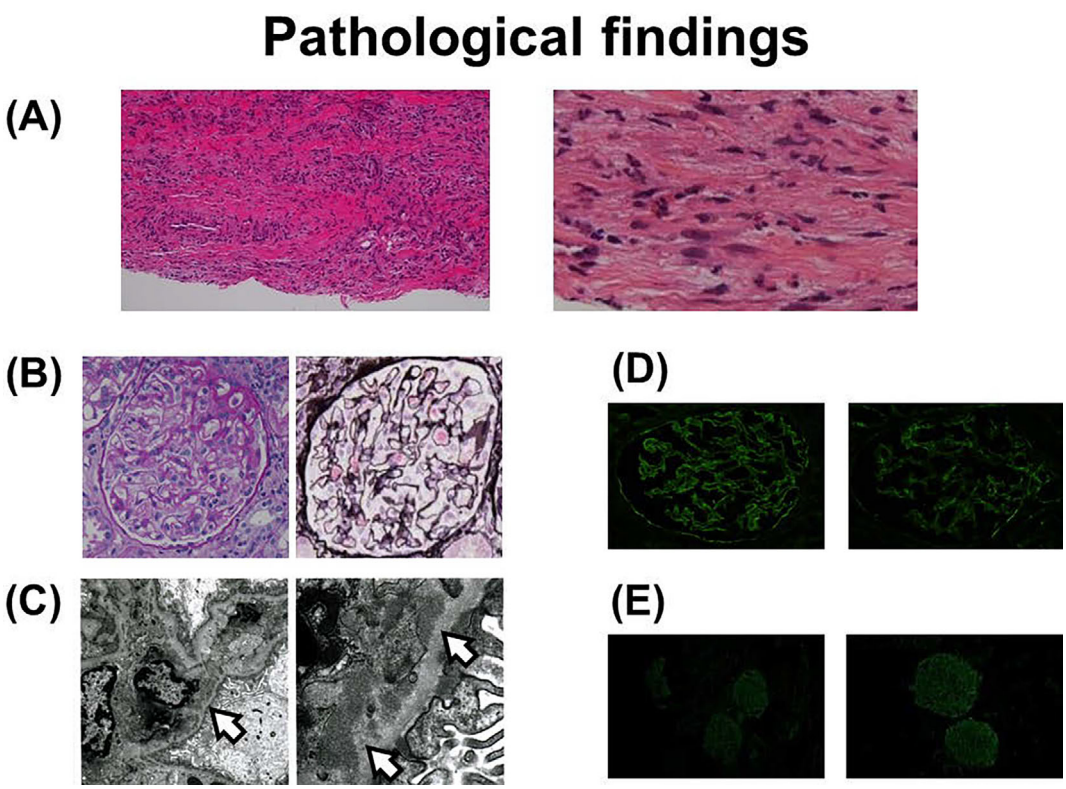

Figure 2. **Pathological findings. (A) The biopsy results of the irregular mass show fibrous tissue with inflammatory cell infiltration containing eosinophils. There are no malignant tumors, no atypical lymphocytes, no granulomatous lesions, and no IgG4-positive plasma cells. Left: Hematoxylin and Eosin (H&E) staining, (original magnification, ×100). Right: H&E staining (original magnification, ×400). (B, C, D, E) Pathological findings of the renal biopsy. (B) Light microscopy shows 18 glomeruli, none of which are globally or segmentally sclerotic and have cellular crescents. There is no infiltrate of IgG4-positive plasma cells in the interstitium with a normal mesangial matrix and no mesangial hypercellularity, no widespread thickening of capillary walls, and no spike formation. Left: Periodic acid-Schiff (PAS) stain (original magnification, ×400). Right: Periodic acid-methenamine-silver (PAM) stain (original magnification, ×400). (C) Electron microscopy shows the presence of extensive subepithelial deposits in the capillary membranes (arrow), with no electron-dense material in the mesangium (original magnification, left ×5,000, right ×30,000). (D) Immunofluorescence microscopy shows diffuse, global, granular capillary wall staining for IgG (+) and C3 (+) (original magnification, ×400. left: IgG, right: C3). (E) The IgG deposits with IgG subclass staining (IgG1, IgG2, IgG3, and IgG4) are predominantly IgG4>IgG1 (original magnification, ×100. left: IgG1, right: IgG4).**

mingham Vasculitis Activity Score (BVAS) version 3 (6), and the initial BVAS was 12.

After the definite diagnosis was made, immunosuppressive therapy with prednisolone (PSL) was started at an initial dosage of 0.8 mg/kg/day (40 mg/day) for RPF, MN, and EGPA (Fig. 3). From the start of PSL, the left abdominal pain gradually improved. In addition, CT of the abdomen showed the disappearance of left hydronephrosis and the irregular mass four weeks later, suggesting remission of RPF (Fig. 1B). However, MN and peripheral neuropathy caused by EGPA had not improved by four weeks after the start of PSL. Urinary proteinuria still exceeded 3.5 g/day, and cyclosporine (CsA) combination therapy was started at an initial dosage of 1.5 mg/kg/day for steroid-resistant nephrotic syndrome. To prevent CsA-induced nephropathy, monitoring of CsA was performed based on the concentration at 2-h post-dose (C2), with a target window of 600-900 ng/mL (7). However, 1 month after the start of PSL and CsA combination therapy (56 days after the start of PSL), urinary proteinuria remained unchanged. Mizoribine (MZB) was then added at an initial dosage of 3 mg/kg/day. After PSL, CsA, and MZB combination therapy, the urinary proteinuria gradually decreased, as did the serum albumin level. The PSL dose was tapered slowly, and 100 days after PSL, CsA, and MZB combination therapy was started (156 days after the PSL therapy started), the urinary proteinuria had decreased to 0.61 g/day, and the serum albumin level had increased to 3.6 g/dL.

The patient was discharged from the hospital 195 days after admission (174 days after the PSL therapy started). On

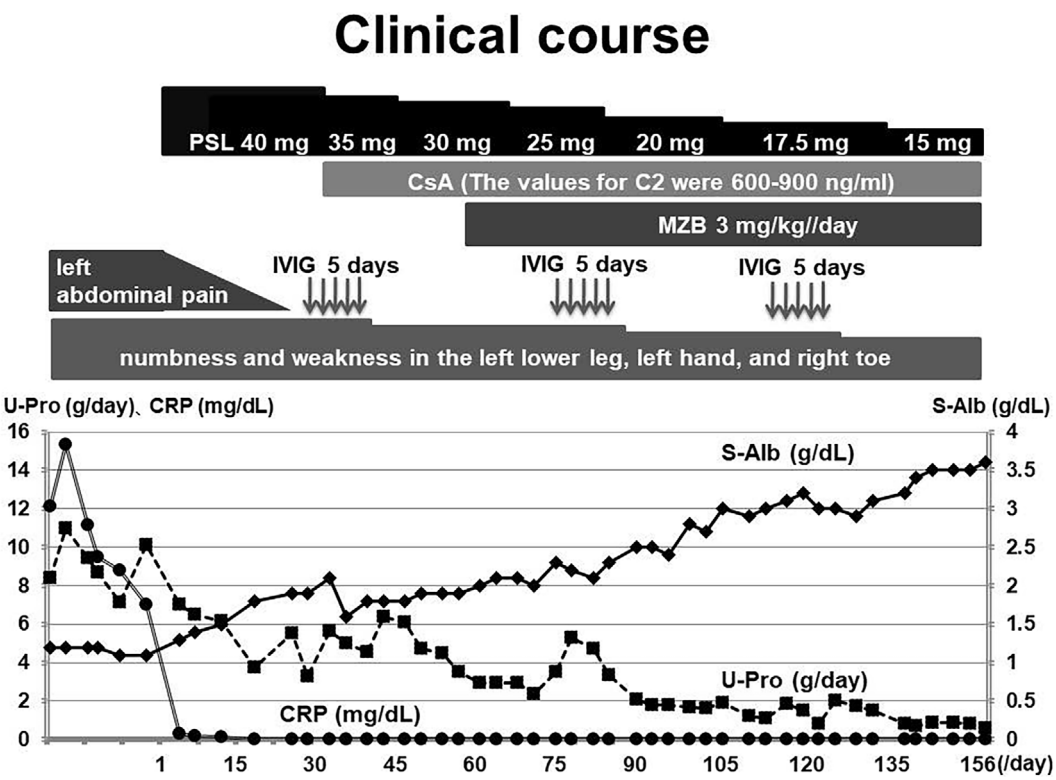

Figure 3. **Clinical course. S-Alb: serum albumin (g/dL, -◆-), U-Pro: urine protein (g/day, -■-), CRP: C-reactive protein (mg/dL, -●-). Monitoring of cyclosporine shows the 2-h post-dose (C2) levels. The C2 values are 600-900 ng/mL.**

reducing the dosage of PSL (month reduction by 2.5-5 mg/day), CR of MN was achieved by 1 year after starting the combination therapy. The dosage of PSL was 5 mg/day as a maintenance dose at 9 months after starting treatment, and CR was further maintained without relapse. The vasculitis was considered to have subsided because the C-reactive protein level and eosinophilia improved rapidly and remained within the normal range after the start of PSL. In addition, symptoms of bronchial asthma or sinusitis was improved, and elapsed without relapse. However, the polyneuropathy remained at four weeks after the start of PSL, and intravenous injection of immunoglobulin (IVIG) was performed for steroid-resistant peripheral neuropathy. The neurological symptoms of polyneuropathy improved slightly after each IVIG treatment but did not improve markedly even after a total of three IVIGs. The BVAS was 0, and the Vasculitis Damage Index (VDI) was 1 (residual symptoms of peripheral neuropathy) at discharge. We achieved CR of EGPA but did not improve the peripheral neuropathy.

Discussion

This is the first report describing a novel case of EGPA simultaneously developing RPF with MN. This case was successfully managed by providing adequate combination therapies according to each disease category, including PSL as a basal immunosuppressive drug for all three diseases, CsA and MZB as additional immunosuppressants targeting MN, and IVIG as an immunomodulating treatment targeting the steroid-resistant peripheral neuropathy caused by EGPA. CR was ultimately achieved for all of these complicated pathologies.

EGPA is an uncommon multisystem disorder characterized by eosinophil-rich granulomatous inflammation and small-vessel vasculitis associated with preceding allergic rhinitis and asthma (8). The incidence of EGPA is estimated to be 0.5-6.8 cases/1,000,000 persons/year (9). EGPA presents a variety of clinical symptoms and typically develops into three sequential phases: the allergic phase, developing allergic rhinitis, sinusitis, and asthma; the eosinophilic phase, with increasing eosinophilic organ infiltration (e.g., lungs, heart, and gastrointestinal system); and the vasculitic phase, presenting with purpura, arthritis, myositis, and peripheral neuropathy. The pathological features of EGPA are necrotizing and leukocytoclastic small-vessel vasculitis with eosinophilic infiltrates and perivascular and extravascular eosinophilic granulomas. In the present case, eosinophilic granulomas in the retroperitoneal tissue were noted, but there were no typical histological findings of vasculitis. Considering the presence of eosinophilia (≥1,500 cells at the previous hospital), the preceding symptoms, including sinusitis and asthma, and the appearance of polyneuropathy, the present patient was definitely diagnosed with EGPA according to ACR criteria and the Lanham criteria (4, 5). Although PSL at the starting dosage of 0.5-1.0 mg/kg/day is generally effective for EGPA (10), early detection and treat-

ment are important for preventing residual symptoms of peripheral polyneuropathy. In the present case, additional IVIG treatment was needed to manage the PSL-resistant polyneuropathy because the complex pathology of EGPA coexisting with both RPF and MN delayed the diagnosis.

RPF is a rare condition characterized by an aberrant fibroinflammatory reaction developing in the peri-aortic retroperitoneum, usually around the infra-renal portion of the abdominal aorta and iliac vessels, often entrapping the ureters and causing obstructive hydronephrosis (11). Although the incidence of RPF is estimated to be less than 0.1-1.3 cases/100,000 persons/year (12), it has been proven that there is a constant association between RPF and other autoimmune inflammatory diseases, including autoimmune vasculitis (13, 14). RPF related to autoimmune vasculitis is often caused by chronic periaortitis, and previous reports suggested that EGPA may cause inflammation of small blood vessels around the aorta, with the inflammation mainly spreading from the abdominal aorta to the iliac arteries (15, 16), similar to the present case. The biopsy specimen of the retroperitoneal mass showed fibrous tissue with inflammatory cell infiltration containing eosinophils in the present case, so RPF was deemed to have actually been caused by EGPA. A good response of RPF to PSL at the starting dosage of 30-60 mg/day has been reported (17), and indeed, RPF immediately improved after the start of PSL in the present case.

MN is a common cause of nephrotic syndrome in adults and is characterized by diffuse thickening of the glomerular basement membrane (GBM) on light microscopy, granular deposits of immunoglobulins (Ig, usually IgG4) and complement (C3) along the capillary walls on immunofluorescence, and subepithelial deposits on electron microscopy (18). Approximately 20-25% of MN cases are secondary to malignancy, infection, drugs, or autoimmune disease, including EGPA and RPF (19). Although the main histological feature of renal involvement in EGPA is a pauci-immune necrotizing crescentic form of glomerulonephritis and/or eosinophilic tubulointerstitial nephritis (20), these findings were not noted in the kidney biopsy specimen of the present case. However, a few previous reports have described the co-occurrence of EGPA and MN without crescents (21, 22), although several cases of MN associated with RPF have also been reported (23). Even so, this is the first case report of MN simultaneously associated with both EGPA and RPF.

In general, PSL therapy at the starting dosage of 0.6-0.8 mg/kg/day combined with other immunosuppressive agents, including CsA and MZB, is used for MN (24). The vasculitis in the present patient was considered to have subsided due to PSL and CsA combination therapy, but such therapy was considered insufficient to ameliorate MN. Thus, PSL and cyclophosphamide (CY) combination therapy was also considered. Although the use of CY can achieve satisfactory therapeutic efficacy, its side effects, including bone marrow suppression, gonadal toxicity, and an increased risk of malignancy, have been a concern. Furthermore, there is a report that MZB is safer with non-inferior efficacy to CY (25), so we selected it for MN. Although this standard therapy alone failed to achieve CR of MN in the present case, interestingly, the additional administration of IVIG provided for steroid-resistant peripheral neuropathy caused by EGPA eventually led to CR of MN. It was previously reported that MN related to chronic neural inflammation was successfully treated by IVIG combined with immunosuppressive therapy (26, 27). Therefore, it appears that the IVIG used for neurological disorders might have contributed to the remission of MN in the present case.

The mechanism underlying the simultaneous onset of these three diseases is unclear. The present case had several features similar to IgG4-related disease (IgG4-RD). IgG4-RD is a systemic fibroinflammatory disease that is typically characterized by elevated serum IgG4 levels and abundant IgG4-bearing plasmacyte infiltration of the involved organs, such as the retroperitoneum, frequently developing RPF (28). In addition, a high proportion of patients with IgG4-RD are reported to have longstanding allergies and peripheral blood eosinophilia (29). Furthermore, IgG4-RD sometimes occurs with MN (30, 31) and neurological disorders (32). Interestingly, an immunohistochemical analysis of PLA2R antibodies in a case of MN with IgG4-RD was negative for all eight biopsies (30). IgG4-RD shows IgG4 levels vary according to differing organ involvement, and are relatively low in patients with predominant RPF (33). Therefore, there might be a possibility that some immunological disorder similar to IgG4-RD latently occurred in this case. Hypocomplementemia may be found in patients with IgG4-RD, especially in those with concomitant renal involvement (34). In fact, laboratory examinations on admission showed hypocomplementemia (C3, 69 mg/dL; C4, 10.9 mg/dL; CH50, 14 mg/dL) in the present case. Hypocomplementemia in the acute phase may have been caused by the consumption of complements due to immune complex formation and their leakage due to nephrotic syndrome. However, 2 months after immunosuppressive therapy with PSL, the hypocomplementemia had improved in the recovery phase (C3, 86 mg/dL; C4, 22.7 mg/dL; CH50, 41 mg/dL), with normal levels persisting subsequently. This clinical course suggests that immunosuppressive therapy with PSL might favorably influence some unknown underlying immunological disorder, similar to IgG4-RD, resulting in the improvement of hypocomplementemia. In addition, the longstanding allergies, peripheral blood eosinophilia, and negative findings for anti-PLA2R antibodies in this case also suggest that IgG4-RD or its similar pathological condition might have been latently present and induced the simultaneous onset of EGPA, RPF and MN. The heterogeneity of the clinical spectra of IgG4-RD and EGPA and the likely pathogenic differences between their subsets may account for the partial overlap between these two syndromes. Once their underlying mechanisms are determined and new diagnostic biomarkers are identified, we may be able to better understand why they overlap and how we can more easily make a

differential diagnosis and provide phenotype-tailored therapies.

In conclusion, this is the first case report of EGPA with mononeuritis multiplex simultaneously developing both RPF causing hydronephrosis and MN leading to nephrotic syndrome. This case was successfully managed by providing adequate combination therapies according to each disease category, leading to CR of all three diseases. We believe that the present case report is highly suggestive and can be applied to a future phenotype-tailored treatment strategy for EGPA with complex pathologies.

The authors state that they have no Conflict of Interest (COI).

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